UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/554,567	09/01/2000	Adriano Aguzzi	6458.US.01	2914

7590 01/12/2007

Steven F Weinstock
Abott Laboratories
100 Abbott Park Road
D 377 AP6D
Abbott Park, IL 60064-6050

EXAMINER	
HORNING, MICHELLE S	
ART UNIT	**PAPER NUMBER**
1648	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
2 MONTHS	01/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450

www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/554,567
Filing Date: September 01, 2000
Appellant(s): AGUZZI ET AL.

Lisa V. Mueller
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/10/2006 appealing from the Office action mailed 09/21/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,165,784 O'Rourke et al Fd-1997

Korth et al. "Prion (PrPsc)-specific epitope defined by a monoclonal antibody" Nature, vol 390 (November 6 1997), pp. 74-77.

Kuroda et al. "Creutzfeldt-Jakob Disease in Mice: Persistent Viremia and Preferential Replication of Virus in Low-Density Lymphocytes" Infection and Immunity, vol 41, no. 1 (July 1983), pp. 154-161.

Manuelidis et al. "Viremia in Experimental Creutzfeldt-Jakob Disease" Science, vol. 200 (June 2 1978), pp. 1069-1071.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 35-37 were rejected und 35 U.S.C 103 as being unpatentable over O'Rourke et al and/or Korth et al in view of Kuroda et al. and/or Manuelidis et al. These claims are drawn to a method of identifying Transmissible Spongiform Encephalopathy (TSE)-infected cells in a test sample. More specifically, claim 35 is drawn to identifying infected B-cells, claim 36 is drawn to identifying infected T-cells and claim 37 is drawn to identifying a combination of infected B and T-cells. The method of claims 35-37 comprises the following steps:

1. obtaining a test sample;

2. collecting B-cells and/or T-cells from the test sample;

3. subjecting the cells above to homogenization;

4. subjecting the cells above to proteinase K digestion;

5. subjecting the said digested cells to SDS Page immunoaffinity chromatography blots;

6. contacting said blots with an anti-PrP antibody, wherein the presence of a signal from said anti-PrP antibody-PrP complex in the sample is indicative of TSE-infected B-cells and/or T-cells; and

7. identifying TSE-infected cells wherein the identification of TSE-infected B-cells is associated with TSE promulgation and primary infection and the identification of TSE-infected T-cells is associated with TSE promulgation and secondary infection.

The limitations above are taught in the prior art as discussed below.

O'Rourke et al. tests for TSE in lymphoid tissue using an antibody that serves as a ligand in various immunoassays, including immunohistochemistry, western immunoblots, and dot blots (see entire document, e.g., "Summary of the Invention"). O'Rourke et al. teach that antibody ligands may be either polyclonal sera or monoclonal antibodies (see entire document, e.g., column 5, especially lines 40-50). The reference teaches the detection steps of starting with tissue homogenization, treatment with proteinase K, separation on polyacylamide gel, transfer to a filter and contacting the filter with a monoclonal antibody to detect the presence of prion in the tissue sample (see column 6, lines 45-55). The reference used TSE containing aliquots equivalent to 125 mg starting material were electrophoresed through a 15% polyacrylamide mini-gel and transferred to PVDF membranes. The filters were developed with monoclonal antibody or a control antibody, goat anti-mouse IgG-HRPO, and a chemiluminescent substrate (see column 10,lines 34-65). The presence of a signal is indicative that prion protein was present in the sample.

Korth et al. detects TSE based upon a monoclonal antibody that is specific for the prion form of PrP (the causative agent in TSEs) versus the cellular form of PrP (see entire document, e.g. Abstract). Korth et al. teach that this antibody can be used to identify the prion form of PrP directly, thus providing a basis for TSE detection in living humans or animals, by lowering the detection threshold needed (see especially paragraph preceding "Methods" on page 77). The reference teach the following steps a) taking brain (tissue) and homogenizing the sample, b) followed by immunoprecipitation with a monoclonal antibody, c) digesting the sample with proteinase K, d) boiling sample in SDS-page buffer, separating on a gel and transferring to membrane (Western Blot), e) detecting the prion on the Western-blot using a rabbit anti-PrP antibody. Complex formation on the Western blot is indicative of the presence of prion in the brain (tissue) sample.

Neither O'Rourke et al nor Korth et al teach the detection of TSE in B cell or in T cells. Kuroda et al. teach that both B cells and T cells can transmit TSE, and Manuelidis et al. teach that it is important to focus on these cellular populations (buffy coat) to increase the sensitivity of assays for TSE infectivity. Both O'Rourke et al. and Korth et al. teach methods of detecting the disease form of prion protein after proteinase K digestion followed by SDS-Page electrophoresis and blotting onto a membrane. One of ordinary skill in the art would have had a high expectation of success in applying the techniques taught by O'Rourke et al. or Korth et al. to the infected tissue disclosed by Kuroda et al. or Manuelidis et al. It would have been obvious at the time the invention was made to improve the sensitivity of the TSE tests by collecting samples containing B

cells and/or T cells and testing for the presence of TSE using an antibody-based system. The ordinary artisan at the time the invention was made would have been motivated to this in order to avoid having to utilize animals via inoculation of a test sample in order to test for infectivity in the B and/or T cell population. The ordinary artisan at the time the invention was made would have reasonably expected that concentrating a cell type known to be infected with the TSE agent would increase the sensitivity of detection assays, including antibody-based assays. In addition, it was well known in the art at the time the invention was made that once an antibody was developed, the antibody could be used with a reasonable expectation of success to detect an antigen on intact cells, as in a buffy coat of whole blood, by either mounting them on slides for immunohistochemical analysis; or by using other techniques well known in the art at the time the invention was made for intact cell analysis with antibodies. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references above.

(10) Response to Argument

Appellants' argument in response to the rejection above contains the following elements which are individually discussed below:

1. neither Kuroda et al. or Manuelidis teach that B-cells and/or T-cells can transmit TSE;

2. there is no motivation to combine the references; and

3. the Korth et al. reference teaches away from the Appellants' invention.

1. Neither Kuroda et al. nor Manuelidis teach that B-cells and/or T-cells can transmit TSE

Appellants assert that the cited references of Kuroda et al. or Manuelidis et al. referred to the disease causing agent as being a virus instead of the instantly claimed prion protein (TSE infecting agent). The "protein only" theory of disease has only recently gained acceptance in the scientific community. The biochemist, Stanley Prusiner, whose discovery provided key insights into dementia-related diseases, won the 1997 Nobel Medicine Prize, Sweden's Karolinska Institute. The institute said Prusiner's work helped the world to understand more about Alzheimer's and Mad Cow disease through his discovery of the prion, a disease-causing agent like bacteria or viruses. Even today there are is still a small group scientists that do not believe the protein only theory. Both of the cited references were published at a time when the prion protein theory of disease was not generally accepted. Even if the references erroneously referred to the disease-causing agent as a virus, this does not detract from the important observations made in the references.

Appellants assert that the inventors are the first to determine the different roles of different components of the immune system by using a panel of immunodeficient mice inoculated with prions. Appellants meticulous dissection of the roles of B and T-cells using more sophisticated methodologies and reagents does not take away from the observations in the prior art that have associated TSE (CJD or scrapie) with the B and T-cells fractions obtained from the spleen of infected animals. In this instance the claims are drawn to a method of detecting the presence of the infective agent in the B and T

cells from a patient test sample. The prior art has shown that the CJD or scrapie agent is associated with these cells. Thus the actual role of transmission of TSE by B-cells and/or T-cells is irrelevant.

2. There is no motivation to combine the references

Appellants assert that because Kuroda et al and Manuelidis et al "mistakenly" believed TSEs were caused by a virus, the skilled artisan would have heavily discounted the disclosures of these two references. Further, the Appellants assert that there is no motivation to combine a reference related to TSEs that discloses an antibody assay for a prion protein with a reference that taught TSEs are viruses. As discussed above, until Stanley Prusiner discovered the prion protein as a disease-causing agent, many believed that TSEs were caused by a virus and many still do. The disparity in the prior art regarding the actual disease-causing agent of TSE is also discussed by the specification of the instant application in the following recitation found on page 3:

"The conversion is believed to result from a conformational rearrangement of PrPc. Some researchers still adhere to the virino hypothesis which holds that the infectious agent consists of a nucleic acid genome and the host-derived PrP, which is recruited as some sort of coat (Dickinson, A.G. and Outram, G.W. Genetic aspects of unconventional virus infections: the basis of the virino hypothesis. Ciba. Found. Symp. 135, 63-83 (1988); Hope, J. The nature of the scrapie agent: the evolution of the virino (Ann. N. Y. Acad. Sci. 724, 282-289 (1994)). Finally, the possibility that the infectious agent is a virus with unusual properties is still upheld by some (Diringer et al., The nature of the scrapie agent: the virus theory. Ann. N. Y. Acad. Sci. 724, 246-

258 (1994); Pocchiari, M. Prions and related neurological diseases. Molec. Aspects. Med. 15, 195-291 (1994); Rohwer, R.G. The scrapie agent: "a virus by any other name "Curr. Top. Microbiol. Immunol. 172, 195-232 (1991)). ".

In summary, regardless of what the investigators think the actual infective agent may be, both Kuroda et al and Manuelidis et al show that the disease-causing agent associated with TSE is present in the B and T-cells of infected animals. Additionally, both Korth et al. and O'Rourke references disclose methods of detecting the infectious agent associated with TSE using antibodies. As stated above, one would have been motivated to combine the teachings of Kuroda et al and Manuelidis et al with those of Korth et al and O'Rourke et al in order to detect the disease-causing agent in B and/or T-cells via a sensitive antibody-based system. Furthermore, the ordinary artisan at the time the invention was made would have been motivated to combine the teachings above in order to avoid having to utilize/sacrifice live animals via inoculation of a test sample. Thus there is sufficient motivation to combine the teachings of the prior art references.

3. The Korth et al. teaches away from the Appellants' invention

The Appellants argue that the Korth et al reference teaches away from the invention. This reference which discloses an antibody that specifically precipitates the abnormal form of prion protein (PrPsc) states that "the identification of an antibody that binds selectively to PrPsc from various species provides a new means to identify PrPsc directly without using proteinase K digestion as a criterion" (page 77). The Appellants argue that the Korth et al reference suggests that a skilled artisan would be able to

avoid the step of proteinase K digestion and thus precipitate the PrPsc protein directly. With this interpretation, the Appellants conclude that, given the instant application is drawn to using both steps of proteinase K digestion and antibody binding of the prion protein within the method, Korth et al teaches away from the Appellants' invention.

This argument is not found persuasive for the reasons below. The method steps include the following: 1. obtaining a test sample; 2. collecting B-cells and/or T-cells from the test sample; 3. subjecting the cells above to homogenization; 4. subjecting the cells above to proteinase K digestion; 5. subjecting the said digested cells to SDS Page immunoaffinity chromatography blots; 6. contacting said blots with an anti-PrP antibody, wherein the presence of a signal from said anti-PrP antibody-PrP complex in the sample is indicative of TSE-infected B-cells and/or T-cells; and 7. identifying TSE-infected cells.

Homogenization of infected B and/or T-cells would result in the accessibility of many cellular proteins, not just prion proteins of normal and abnormal conformations. Thus, given that proteinase K is a broad enzyme, this enzyme would also degrade other cellular proteins. Following digestion with this enzyme, the digested cells are subjected to SDS Page immunoaffinity chromatography blots in which one could then determine the size of the protein by the distance of migration through the SDS Page. Because the broad enzyme does not digest abnormal prion proteins while digesting others including the normal prion protein, proteinase K improves the isolation of abnormal prion protein from other cellular proteins on the SDS Page. Thus one would have been motivated to treat the homogenized sample with proteinase K because an increased isolation of

abnormal prion protein would lead to a greater signal to noise ratio following contacting the blots with an anti-PrP antibody.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Michelle Horning

Conferees:

Bruce Campell, SPE 1648

Shanon Foley, SPE 1645

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600